A CLINICO-PATHOLOGICAL STUDY OF ACUTE GLOMERULONEPHRITIS IN EAST AFRICAN CHILDREN

BY

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The assessment of disease incidence in Uganda, an emerging but still young country, presents many problems. Information about a disorder such as acute glomerulonephritis, which has a high spontaneous recovery rate and may present atypical clinical features, is particularly liable to be misleading. The evidence that already exists is conflicting. Luder (1958) saw no cases of 'Type I' nephritis in African children during two years' work at Mulago Hospital; on the other hand, Musoke (1961), analysing admissions to the children's wards during 1959, reported that 8 out of 18 renal admissions were for acute nephritis. In a retrospective survey of admissions to the medical wards during 1957, Shaper and Shaper (1958) found only 3 among 131 patients with renal disease.

In necropsy surveys, Raper (1953) reported only 15 instances of Type I nephritis in six years, while Allison (1962) found no cases of acute nephritis and only 13 cases of chronic glomerulonephritis among 272 necropsies showing renal disease. However, the high recovery rate in acute nephritis and the low necropsy rate among children in Uganda combine to render post-mortem figures misleading. Nevertheless, the prevalence of 'proliferative glomerulitis' in earlier necropsy surveys (Hennessey, 1939; Davies, 1949) suggests that a background of antecedent acute nephritis must exist.

With the aid of renal biopsy, Leather (1960) found that glomerulonephritis was the commonest type of renal disease during the first four decades and was present in 12 of 13 children studied. Fortunately, the histological features of acute diffuse glomerulonephritis are well defined. In this paper we report the results of a prospective study, in which a diligent search for clinical evidence suggestive of glomerulonephritis was combined with the appraisal of renal biopsy material, undertaken in the hope of obtaining a better understanding of the incidence, clinical patterns, and pathological features of the disease in Uganda.

Material and Methods

Between August 1960 and July 1962, 45 negro children with evidence of renal disease, based on clinical and laboratory findings, were studied by means of percutaneous renal biopsy: 23, in whom a histological diagnosis of acute diffuse glomerulonephritis was made, are included in this paper, and a further child, in whom the diagnosis was made at necropsy, has been added (Table 1). Investigations were carried out as follows.

Urine analysis. On admission, at least one urine specimen from every child was examined by one of us. Quantitative 24-hour protein output estimations were attempted but failed or were considered unreliable owing to difficulty in collection of specimens. However, the protein concentration was estimated in specimens from every child and the centrifuged deposit was examined microscopically.

Bacteriology. Throat swabs were taken from 20 children and were cultured on blood agar medium. Later in the series, haemolytic streptococci were grouped when isolated.

Serology. Antistreptolysin-O (ASO) titres were estimated in 20 of the patients.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>CLINICAL PRESENTATION OF 46 AFRICAN CHILDREN WITH RENAL DISEASE, INCLUDING 24 DIAGNOSED HISTOLOGICALLY AS ACUTE DIFFUSE GLOMERULONEPHRITIS (AGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Presentation</td>
<td>Number of Biopsies</td>
</tr>
<tr>
<td>Acute haemorrhagic nephritis</td>
<td>18</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>35</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>3</td>
</tr>
<tr>
<td>Detected on routine urinalysis</td>
<td>4</td>
</tr>
</tbody>
</table>

* Includes one child diagnosed at necropsy.

* Present address: Department of Paediatrics, Guy's Hospital, London, S.E.1.
**Table 2**

**PRESENTING SYMPTOMS IN 24 CHILDREN WITH AGN**

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling and dark or bloody urine</td>
<td>11</td>
</tr>
<tr>
<td>Swelling only</td>
<td>10</td>
</tr>
<tr>
<td>Dark or bloody urine only</td>
<td>2</td>
</tr>
<tr>
<td>Oliguria</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>13</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Joint pains</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 3**

**MAIN PHYSICAL FINDINGS IN 24 CHILDREN WITH AGN**

<table>
<thead>
<tr>
<th>Physical Findings</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema, slight to moderate</td>
<td>17</td>
</tr>
<tr>
<td>Oedema, gross, with ascites</td>
<td>5</td>
</tr>
<tr>
<td>Macrophagic haematuria</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension (blood pressure recorded in 3)</td>
<td>14</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>6</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>5</td>
</tr>
<tr>
<td>Non-respiratory sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Acute rheumatism</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 4**

**RELATION BETWEEN ASO TITRE AND CLINICAL MANIFESTATIONS**

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>ASO titre (units/ml.)</th>
<th>Not Recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;200</td>
<td>166</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Neptrophic</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* One child (Case 3) also had acute rheumatism; ASO titre was 100 units ml. 98 days from onset when second biopsy showed recovery.

**Table 5**

**DETAILS OF 4 CHILDREN PRESENTING WITH NEPHROTIC SYNDROME**

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Case 8(M)</th>
<th>Case 9(M)</th>
<th>Case 13(F)</th>
<th>Case 22(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Poor</td>
<td>Good</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroscopic haematuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (g. 100 ml.)</td>
<td>5.3</td>
<td>4.2</td>
<td>3.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Albumin (g. 100 ml.)</td>
<td>1.7</td>
<td>2.1</td>
<td>1.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood urea (mg. 100 ml.)</td>
<td>100</td>
<td>138</td>
<td>106</td>
<td>185</td>
</tr>
<tr>
<td>Haemoglobin (g. 100 ml.)</td>
<td>5.5</td>
<td>13.0</td>
<td>5.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Hookworm</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Malaria</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Table 6**

**DETAILS OF 3 CHILDREN PRESENTING WITH CONGESTIVE CARDIAC FAILURE**

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Case 18(F)</th>
<th>Case 21(M)</th>
<th>Case 24(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema (O-1)</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blood urea (mg. 100 ml.)</td>
<td>55</td>
<td>30</td>
<td>109</td>
</tr>
<tr>
<td>Haemoglobin (g. 100 ml.)</td>
<td>6.7</td>
<td>8.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Hookworm</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 7**

**DETAILS OF 3 CHILDREN DETECTED ON ROUTINE URINALYSIS**

<table>
<thead>
<tr>
<th>Age (yr.)</th>
<th>Case 7(F)</th>
<th>Case 17(F)</th>
<th>Case 19(M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema (O-1)</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood urea (mg. 100 ml.)</td>
<td>28</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Haemoglobin (g. 100 ml.)</td>
<td>11.7</td>
<td>6.4</td>
<td>7.6</td>
</tr>
<tr>
<td>Presenting illness</td>
<td>Acute Sickle cell Anaemia</td>
<td>Hookworm Anaemia</td>
<td></td>
</tr>
</tbody>
</table>

**Blood Chemistry.** Blood urea levels were estimated on admission in every patient, and were subsequently repeated in children whose initial levels were raised. Serum protein estimations, together with serum protein paper electrophoresis, were carried out in 23 and serum cholesterol in 19 cases.

Haemoglobin estimations, reticulocyte counts, blood smears for malarial parasites, sickling preparations and haemoglobin electrophoresis if indicated, and stool concentrations for parasites and ova were carried out as routine investigations on all admissions. The results will be given only in selected cases where they appear to influence symptoms.

**Percutaneous Renal Biopsy.** This was performed on all but the last patient, who died shortly after admission to hospital and was examined post mortem. In 3 children two biopsies were performed, and in a further 2 children three biopsies, at intervals. The biopsy instrument and technique employed have been described elsewhere (White, 1962, 1963). No serious complications of biopsy were encountered in this series, but one patient, a 26-day-old infant, died 23 hours later from causes unrelated to the performance of renal biopsy (White, 1963).

The biopsy material was immediately transferred to Susa fixative and embedded in paraffin. As a routine, serial sections were cut at 2-5 μ and stained with haematoxylin and eosin and by the periodic acid-Schiff technique. In selected cases Weigert's iron haematoxylin and van Gieson, and Mallory's trichrome stains were also used.

**Results**

**Clinical Manifestations.** Clinical details of the 24 patients, 12 boys and 12 girls, are given in Tables 2-7. Their ages ranged from 1 month to 15 years (Fig. 1), 19 (79%) being under 5 years.

The presenting symptoms are summarized in Table 2 and the main physical findings in Table 3. Swelling, the commonest complaint, was volunteered in 21 and oedema was found on examination in 22,
ACUTE GLOMERULONEPHRITIS IN EAST AFRICAN CHILDREN

being slight to moderate in 17 and gross in 5 children who also had ascites. The passage of dark or blood-stained urine was not usually volunteered as a complaint but was admitted on questioning by the parents of 13 children, in 11 of whom there was associated swelling. Macroscopic haematuria was confirmed on admission in all 13, and was observed in 2 other children in whom its occurrence was denied by the mothers. Thus, oedema and macroscopic haematuria occurred together in 14 patients, oedema alone in 8, haematuria alone in 1, and neither in 1. Hypertension, assessed according to the figures of Haggerty, Maroney, and Nadas (1956) for children of different ages, was observed in 14 out of 23 children in whom the blood pressure was recorded. It was associated invariably with oedema and in 10 instances with gross haematuria. Congestive cardiac failure occurred in 6 children, of whom 4 were hypertensive and 3 had gross haematuria: all had moderate or severe anaemia, with haemoglobin levels ranging from 3.7 to 8.8 g./100 ml. Sixteen children gave histories of antecedent illness suggesting upper respiratory infection, e.g. pyrexia, cough, and abdominal pain, and 6 were found to have acute tonsillitis on admission. Two had infected skin lesions, 1 had septicaemia following umbilical sepsis, and 1 child was originally admitted with acute rheumatism.

Urinalysis. Protein, varying from 30 to more than 1,000 mg./100 ml. of urine, red blood cells, and polymorphonuclear leucocytes were present in the urine of all the patients on admission, and granular casts were found in 17.

Bacteriology. β-haemolytic streptococci were isolated in 8 out of 20 throat swabs; in 6 of these the group was not specified, and in the remaining 2 it was specified as ‘not group-A’. In no instances were group-A haemolytic streptococci positively identified.

Serology. ASO titres exceeded 200 units/ml. in 13 out of 20 children in whom results were obtained. Cases 10 and 17 had titres of 166 units/ml., which can be accepted as abnormal levels for children of their age, since Potter and Lober (1961) were unable to demonstrate titres as high as 100 units/ml. in healthy children between 2 months and 2 years of age. Although the numbers are small it is perhaps noteworthy that a higher proportion of raised titres occurred in patients presenting with macroscopic haematuria than in the other three clinical groups (Table 4).

Blood Chemistry. Blood urea levels were initially raised above 40 mg./100 ml. in 12 children, and in most instances the rise was moderate and transient. However, in Case 12, whose haematuria began eight weeks before admission, the first reading obtained was 321 mg./100 ml.

The serum proteins showed appreciable variation, according to the patients' nutrition and the occurrence of local infections such as hookworm and malaria. No characteristic electrophoretic pattern was observed, though 11 patients showed a slight rise of α₁-globulin. Four children presenting with the nephrotic syndrome showed striking hypoalbuminaemia (Table 5).

Serum cholesterol levels ranged from 61 to 247 mg., the mean being 142 mg./100 ml.

Variations in the Clinical Pattern. Fourteen patients presented in the classical manner, with macroscopic haematuria in all cases and slight to moderate oedema in 13: 9 were hypertensive, 7 had urea retention, and 3 had congestive cardiac failure.

Four children were found, on admission, to have gross oedema with ascites, proteinuria of more than 1%, and hypoalbuminaemia, and were therefore classified clinically as nephrotics (Table 5). In Cases 8, 13, and 22, however, poor nutrition and severe hookworm infection, with haemoglobin levels of only 5-6 g./100 ml., undoubtedly contributed to the hypoproteinaemia and oedema. All three were hypertensive: Case 13 had urea retention and Case 22 macroscopic haematuria, a feature that was not volunteered as a symptom but discovered on admission. The fourth case (Case 9), on the other hand, was a breast-fed and well-nourished male infant, and had neither hookworm nor malaria.

Case 9. Swelling began in the scrotum at the age of 8 days and extended rapidly. When admitted on the fourteenth day he was found to have gross oedema and ascites. The umbilical stump was slightly swollen and

![Fig. 1.—The age incidence of 24 children with acute glomerulonephritis.](http://adc.bmj.com/)

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inflamed. Both kidneys were easily palpable. The blood pressure was not recorded. The urine showed protein 10%, red blood cells, and leucocytes. The ASO titre was greater than 333 units/ml. Biochemical data are shown in Table 5. With a provisional diagnosis of septicaemia, secondary to umbilical sepsis and complicated by the nephrotic syndrome, possibly due to renal vein thrombosis, he was treated with intramuscular penicillin and streptomycin, and subsequently oral tetracycline. However, his condition did not improve and on the 24th day he had two convulsions. The right kidney was biopsied without difficulty on the 27th day; he died on the following day and necropsy confirmed the biopsy finding of acute diffuse glomerulonephritis, while revealing no evidence of operative trauma that could have accounted for death (White, 1963). There was a collection of pus in the umbilical vein, from which a coagulase-positive Staph. aureus was cultured, with metastatic abscesses and extensive pulmonary alveolar haemorrhage, believed to have been the immediate cause of death.

Three children were admitted on account of congestive cardiac failure (Table 6). Oedema was gross only in Case 24 but all three had ascites. Cases 18 and 21 were hypertensive. All had proteinuria and microscopic haematuria, and granular casts were found in the urine of Cases 18 and 21. They were all undernourished and anaemic, and Cases 18 and 21 were infected with Ancylostoma duodenale. In Case 24 cardiac failure was severe enough to cause death on the second day of admission, and the diagnosis of glomerulonephritis was revealed at necropsy.

Three children were found to have protein, red blood cells, and granular casts in their urine on routine analysis (Table 7). Case 7 was admitted with acute tonsillitis, and Cases 17 and 19 with anaemia and slight oedema, their provisional diagnosis being hookworm infection. This was confirmed in Case 19 but not in Case 17, who was found to have sickle-cell anaemia. All had normal blood pressure levels and the highest blood urea level recorded was 42 mg./100 ml. in Case 19.

### Histological Findings in Initial Biopsies

Renal biopsy was performed in 22 patients, necropsy in 1, and both in 1, from four to ninety days after the onset of the acute attack. In 5 patients more than one biopsy was done. The changes in the individual patients are summarized in Table 8.

### Glomerular Tufts

The principal histological feature, common to all the patients, was cellular proliferation of the glomerular tuft, which usually led to an increase in the size of the whole glomerulus and frequently to obliteration of the capsular space (Fig. 2). Analysis of the changes in the glomerular tufts in thin sections stained by the periodic acid-
Schiff technique suggested that the proliferation was mainly of endothelial cells, although the possibility that mesangial cells were also increased could not be excluded. The increased cellularity, demonstrated by the larger number of nuclei, was accompanied by an excess of pink-staining material in haematoxylin and eosin sections. The appearances suggested that this was principally due to swelling of the endothelial cell cytoplasm and, in thin sections, it could often be seen almost filling the lumen of the capillaries. In many of the biopsies mitotic figures were seen in occasional glomeruli. There did not appear to be any gross alteration of the epithelial cells of the tuft, although they were occasionally swollen and sometimes contained hyaline droplets. The exceptions to this were seen in those cases where there was proliferation of the Bowman's capsules, forming cellular crescents; in these specimens swelling and proliferation of tuft epithelial cells were often seen.

The other feature present in all cases was exudation of polymorphonuclear leucocytes into the glomerular tufts (Fig. 2). The appearances suggested that the polymorphs were adherent to the swollen endothelial cell cytoplasm within the capillary lumens. The basement membrane usually showed no abnormality, although occasionally there seemed to be fraying or oedema, and in the specimen from Case 12, where the lesion was progressive, there was a greatly increased network of basement membrane fibrils in the tufts. In some of the biopsies these changes in the glomerular tufts were the only abnormalities found. Sclerosis of the tufts was a prominent finding only in Case 12, although occasional sclerotic glomeruli were seen in five other specimens.

**Bowman's Capsules.** In 9 biopsies the epithelial cells of Bowman's capsules showed swelling and proliferation and in several there were occasional glomeruli in which this proliferation was sufficient to justify the term crescent. In 3 patients frank cellular crescents were seen in numerous glomeruli, and in one child (Case 4) they were noted as early as six days after the onset of symptoms. In several other biopsies occasional glomeruli contained fibrotic crescents, and in Case 24, who was not biopsied, detailed examination at necropsy showed them in only 1 in about every 50 glomeruli. In Case 12 many glomeruli showed adhesions between crescents and fibrils arising from the basement membrane of the abnormal capillary tufts, leading to obliteration of the capsular spaces and complete glomerular sclerosis.
In two specimens tubularization of the capsular epithelium was observed, the cells resembling those of the proximal tubules.

**Tubules.** In 19 of the initial biopsy specimens red blood cells were seen in the tubular lumens. Tubular changes were not usually striking and consisted principally of dilatation, with flattening of the epithelial lining of both proximal and distal tubules. Necrosis was seen in two instances only. Close scrutiny of the tubules showed, however, that in several patients there was increased mitotic activity, suggesting regeneration of damaged epithelial cells.

**Interstitial Tissue.** Ten cases showed interstitial oedema and patchy infiltration with inflammatory cells. This was usually associated with lesions in the tubules and Bowman’s capsules. A fairly constant feature in this series was the presence of foci of plasma cells in the interstitial tissue. Occasional eosinophils and polymorphs were also seen. Except in Case 12, who had rapidly progressive glomerulonephritis, fibrosis was not a notable feature and there were no changes in the arterioles.

**Assessment of Renal Damage.** In an attempt to correlate the over-all histological features with some of the clinical and biochemical abnormalities, the patients have been placed into one of four grades of histological damage. The grading of the initial biopsies in individual patients is shown in Table 8. The criteria of assessment, shown below, are dependent on changes in the Bowman’s capsules, tubules, and interstitial tissues. Cellular proliferation of glomerular tufts and polymorphonuclear exudation are, of course, common to all grades.

**Grade I:** No significant widespread changes in Bowman’s capsule, the tubules, or interstitial tissue (14 patients).

**Grade II:** Focal changes in the interstitial tissue consisting of oedema and inflammatory cell infiltration, usually associated with tubular dilatation and/or proliferation of the cells of Bowman’s capsule, forming occasional crescents (7 patients).

**Grade III:** As II, but with more widespread tubular and interstitial changes, and more numerous crescents (2 patients).

**Grade IV:** As III, but with numerous crescents and extensive glomerular sclerosis (1 patient).

**Histological Findings in Repeat Biopsies.** Repeat biopsies were performed on 5 patients (Table 9), 3 of whom showed Grade I changes on their initial specimens. Case 3 was re-biopsied 98 days after the onset of illness, when the specimen was normal apart from residual proliferation in occasional glomeruli and the presence of red blood cells in some of the tubules. In Case 13 a second biopsy, at 69 days, showed slight proliferative change in most of the glomeruli while a third, at 137 days, was virtually normal. Case 21 had a second biopsy at 44 days that showed residual proliferation in the tufts and occasional foci of inflammatory cell infiltration in the interstitial tissues. From these findings it appears that resolution of the lesions in those with Grade I damage is complete in about 80-120 days from the onset of the illness.

Case 15, who showed Grade II lesions initially, had biopsies performed at 7, 65, and 126 days, and in the last specimen there were still significant changes consisting of minimal proliferation of some of the glomerular tufts, slightly increased cellularity of Bowman’s capsules, and occasional sclerosing glomeruli. There was, however, complete resolution of the tubular and interstitial changes, and our impression was that activity was subsiding and that the patient would probably survive with a number of
ACUTE GLOMERULONEPHRITIS IN EAST AFRICAN CHILDREN

scarred and functionless glomeruli, although the possible development of a latent phase, followed by chronic nephritis, could not be ruled out at this stage.

Case 8, in Grade III, was biopsied after 15 and 59 days. Marked changes were found in both specimens and the only significant difference was the greater frequency of sclerosing glomeruli and fibrous crescents in the second biopsy, suggesting that a progressively destructive process was occurring.

Correlation of Structure and Function. In an attempt to correlate structure and function we have tabulated the relation between the four grades of renal damage and some of the clinical and laboratory findings. From Table 10 it can be seen that there was an even distribution of normal and raised blood pressures, microscopic and macroscopic haematuria, slight to heavy proteinuria, and insignificant and raised antistreptolysin titres among patients showing Grade I histological changes. Grades II-IV changes, however, were more often associated with hypertension, gross haematuria, heavy proteinuria, and raised antistreptolysin titres. Since, however, only 3 patients fall into Grades III and IV, caution is needed in drawing any conclusions from the findings.

The wide range of blood urea levels seen in patients with Grade I histological changes overlaps the levels in Grade II and III (Fig. 3), and the highest levels in these three grades were, in fact, obtained from two Grade I patients, Cases 9 and 24, both of whom died. The one patient in Grade IV (Case 12) had a blood urea of 321 mg./100 ml. on admission, but it fell gradually and fluctuated between 46 and 60 mg. during her last month in hospital.

Treatment, Follow-up, and Prognosis. Bed-rest was encouraged while gross haematuria continued, but owing to the nursing shortage a strict régime was not possible and many patients were discharged prematurely to make room for more seriously ill children. Dietary protein was not usually withheld as nephritis was often complicated by malnutrition and hookworm. Intramuscular penicillin was given routinely. Subsequent out-patient attendance was poor and domiciliary visits were considered impracticable. Only 8 out of 22 survivors were followed up for more than eight weeks from the onset of illness and further renal biopsies were performed on 5 of them (Table 9).

Three of these were from patients initially labelled Grade I. Two were normal and one showed appreciable resolution of the changes. The Grade II patient showed minimal abnormalities on her third biopsy and microscopic haematuria continued. The remaining 15 survivors in these grades would probably have recovered, but limited follow-up precluded attempts to prognosticate. In Grades III and IV, however, the prognosis was clearly poor. Case 4 ran away during a severe, early relapse, and Case 12 had both urinary abnormalities and impaired renal function. In Case 8 haematuria persisted and the second biopsy showed deterioration.

Discussion

When comparisons are made with previous reports from Uganda (Luder, 1958; Shaper and Shaper, 1958) there appears to have been a dramatic increase in the incidence of acute nephritis in children in the past few years. The problem arises as to whether this increase is a real one or reflects better case finding. Symonds (1960) recorded an increasing incidence of nephritis in Trinidad in 1958, reaching epidemic

<table>
<thead>
<tr>
<th>Blood pressure (23 patients)</th>
<th>Histological Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>I  II  III  IV</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>7  2  —  —</td>
</tr>
<tr>
<td>Microscopic</td>
<td>6  5  2  1</td>
</tr>
<tr>
<td>Proteinuria (mg. 100 ml.)</td>
<td>30–100 100–300 &gt;300</td>
</tr>
<tr>
<td>ASO titre (units ml.)</td>
<td>&lt; 166 166 &gt; 200</td>
</tr>
<tr>
<td>Not recorded</td>
<td>3  1  —  —</td>
</tr>
</tbody>
</table>

* One patient had acute rheumatism.

Fig. 3.—The relation between histological grading and blood urea levels on admission to hospital.
proportions and later subsiding. Rammelkamp and Weaver (1953) observed that the attack rate varied from year to year and epidemics are occasionally reported in temperate climates (Siegel, Rammelkamp and Grifeath, 1955; George, McDonald, Payne and Slade, 1958; Pleydell and Hall-Turner, 1958). However, in the series reported here there was no significant seasonal variation and the geographical distribution paralleled the population density. Moreover, there appears to have been no decline in the occurrence of acute nephritis since the completion of this study. The evidence suggests that this recent increase might be explained by greater use of the medical services by the local population, better screening by medical assistants, increased awareness of the condition by those informed of our prospective survey, the insistence upon routine urinalysis in the wards and the use of renal biopsy as an infallible diagnostic procedure.

From the published material it appears that the nephrotic syndrome is commoner than acute 'haemorrhagic' nephritis in tropical Africa (Luder, 1958; Lauckner, Rankin and Adi, 1961), in contrast to South Africa where, as in the temperate zones of the northern hemisphere, acute nephritis is much the commoner (Furman, 1955; Uys, 1956). This has recently been amply confirmed in Nigeria, where Hendrickse and Gilles (1963) collected 156 children with the nephrotic syndrome and only 22 with acute nephritis during the same period. In Uganda, on the other hand, our own observations (Table I) suggest that the incidence of 'classical' acute nephritis is more than half that of the nephrotic syndrome. However, since the nephrotic syndrome is now recognized as denoting a clinical and biochemical pattern rather than a single pathological entity, a purely clinical classification of nephritis is no longer sufficient, and racial and geographical evaluation must, therefore, hinge on both the clinical and pathological findings.

The histological features in the initial renal biopsy and post-mortem specimens from our 24 cases were all characteristic of acute, diffuse glomerulonephritis. These findings consist essentially of swelling of the glomerular tufts due to proliferation of the endothelial and possibly mesangial cells, swelling of the endothelial cell cytoplasm and infiltration by polymorphonuclear leucocytes. Several specimens showed proliferative changes in Bowman's capsules, with crescent formation, and these changes were frequently associated with evidence of tubular damage and interstitial infiltration or fibrosis. The more severe capsular changes were usually paralleled by striking tubular and interstitial lesions. These features are similar to those found in renal biopsy specimens from adults with acute glomerulonephritis (Hutt, Pinniger and de Wardener, 1958). It is now generally accepted that the histological features described above denote a β-haemolytic streptococcal aetiology, and it is apparent that the disease can be recognized at a later stage by the persistence of endothelial proliferation in the lobular stalk region of the glomeruli (Jennings and Earle, 1961; Lawrence, Pollak, Pirani and Kark, 1963). Two specimens also showed striking tubularization of the capsular epithelium. The significance of this change is not understood. Hutt et al. (1958) observed it in adults with acute nephritis but Trowell, Davies, and Dean (1954) stated that the capsular epithelium was frequently cubical in East African children dying from kwashiorkor.

In this series serological evidence of recent β-haemolytic streptococcal infection was obtained in 15 out of 20 patients (75%) in whom the ASO titre was estimated; a further child, whose ASO titre was not estimated, also had acute rheumatism. ASO titres of 200 units/ml. or more have been reported in 94% of North American children suffering from acute nephritis (Lyttle, Seegal, Loeb and Jost, 1938) and in 62% of South African children of non-European origin (Levin and Yoffe, 1960). However, a titre of less than 200 units ml. of blood does not preclude streptococcal infection; this has been substantiated by Jennings and Earle (1961) who demonstrated raised titres of antistreptokinase, antihyaluronidase and streptococcus type 12 antibodies in the serum in the presence of low ASO titres. The site of streptococcal infection in the cases reported here is uncertain; in our experience throat swab culture techniques in routine use proved unreliable. Two children had impetiginous skin lesions which may have been the source of infection. Blumberg and Feldman (1962) found impetigo in 68% of children with acute nephritis while only 3 out of 63 throat swabs gave positive cultures. Davies (1949) and Symonds (1960) have drawn attention to the skin as a likely source of streptococcal infection in negro children.

The age incidence in the present series is unusually low: 79% of the children were under 5 years old. Levin and Yoffe (1960) found that 63% of non-European children in South Africa were under 6 years old, while about 60% of Symonds' (1960) Trinidad negros were under 5 years. In British and North American children, on the other hand, the incidence rises steeply at 3 years and falls at 9 to 10 years, less than 50% of cases occurring in children under 5 years old (Payne and Illingworth, 1940; Burke and Ross, 1947; Lewis, 1955; Blumberg and Feldman, 1962). The higher frequency of young
patients in underdeveloped countries parallels the age incidence of infectious diseases such as poliomyelitis (Gear, 1958), presumably reflecting early exposure to β-haemolytic streptococcal infection.

Neonatal glomerulonephritis is very rare. Thompson (1951) described an infant dying at 29 days with oedema, cardiac failure, and albuminuria, and Collins (1954) reported a neonatal death at 90 hours, associated with oedema and jaundice. At necropsy the kidneys in both cases showed similar features, consisting principally of increased cellularity and hyalinization of the glomerular tufts which were frequently adherent to capsular crescents, and tubular dilatation with vacuolation of the proximal tubular epithelium. Claireaux and Pearson (1955) suggested that these were probably cases of intrauterine pyelonephritis and gave a detailed description of a further infant who died with respiratory distress 10 hours after birth. The kidneys showed striking tubular dilatation, with colloid casts, and the glomeruli, which were reduced in number to one-third, showed considerable atrophy and percapsular fibrosis. Some contained crescents that obliterated the capsular spaces. Inflammatory cell infiltration and interstitial fibrosis were conspicuous only in the cortex. They claimed that this was another example of chronic pyelonephritis, but were able to provide neither bacteriological support nor a convincing explanation of the extensive glomerular changes. They also remarked that the infant’s mother had had a sore throat twice during pregnancy and that her ASO titre was 200 units ml. three months after confinement.

Kunstadter and Rosenblum (1954) described a baby with the nephrotic syndrome, beginning at 9 days and associated with severe anaemia: this infant died at 72 days and, at necropsy, the glomeruli showed hyperaemia and increased cellularity, with occasional capsular proliferation and adherence to the tufts. In the only newborn infant in our series, who also presented clinically as a nephrotic, the kidneys showed, on biopsy and at necropsy, the typical appearance of acute diffuse glomerulonephritis—including polymorphonuclear exudation, a feature not mentioned in previous reports. Although the ASO titre exceeded 333 units ml., it is unlikely that he could have manufactured his own antibodies to this extent (Lippard and Johnson, 1935; Potter and Lorber, 1961). It is, however, known that antistreptolysins are capable of crossing the placental barrier, and cord blood levels usually correlate with the mother’s titres (Lippard and Wheeler, 1936). In our case the mother’s titre was unfortunately not estimated. It is tempting to speculate that streptococcal antibodies that have entered the foetal circulation transplacentally may play a role in the aetiology of intrauterine glomerulonephritis.

The commonest presenting symptom in our patients was swelling of the body; oedema was confirmed in 22 children (91·7%). In tropical Africa, the mortality associated with oedema in children is well known to parents, although knowledge of the main causes, i.e. kwashiorkor and hookworm disease, eludes them, and medical advice is nowadays sought increasingly for this symptom. Four patients showed features of the nephrotic syndrome and, although there were atypical features such as haematuria, hypertension, and azotaemia, as well as other contributory factors, such as poor nutrition and hookworm infection, these cases might well have been diagnosed as ‘nephrosis’ or ‘Type II nephritis’ before the advent of renal biopsy. Wilson and Heymann (1959) reported five children suffering from acute nephritis who presented as nephrotics and, in the 22 children recently described by Hendrickse and Gilles (1963), marked oedema and hypoalbuminaemia were constant features. It is evident that, in a country where there are multiple causes of hypoproteinaemic oedema, careful clinical and laboratory assessment is necessary before classifying oedema, proteinuria, and hypoproteinaemia simply as ‘Type II nephritis’.

Haematuria was volunteered as the sole complaint in only two instances and was actually denied by the mothers of two children in whom it was observed in hospital. The two probable explanations are, first, the local custom of micturating on the soil (which in Uganda is red) or, less often, into pit latrines; and secondly, the belief, prevalent amongst the Baganda tribe, that the simultaneous occurrence of oedema and haematuria is due to gonorrhoea in the father (F. J. Bennett, 1963, personal communication).

Congestive cardiac failure has long been recognized as a feature of acute nephritis (Goodhart, 1879; Burke and Ross, 1947; Davies, 1951). Levy (1930), Brod (1949), and Sharpey-Schafer (1955) have drawn attention to its occurrence in the absence of leading symptoms such as haematuria, and indeed occasionally with normal urine. Histological proof of the diagnosis in such cases has recently been provided by Hutt et al. (1958) and Blumberg and Feldman (1962), as well as in 3 patients in this series. Congestive cardiac failure was a feature of the illness in 3 other children who, however, also had haematuria. Of the 6 with heart failure, 4 were hypertensive. Hookworm anaemia was presumably a contributory factor in 4 who were found to be infected, but only Case 1 had a haemoglobin level of less than 4·0 g. 100 ml., as in the patients of Somers (1959) in whom hook-
worm was the sole cause of reversible cardiac failure.

The urine of symptomless patients convalescent from scarlet fever and acute tonsillitis is frequently found to contain an increased amount of protein, cells, and casts (Lyttle, 1933; de Wesselow, Goadby, and Derry, 1935), and it has been suggested that mild attacks of post-streptococcal nephritis are common. Siegel et al. (1955) have correlated these findings with proof of type 12 haemolytic streptococcal infection. Our biopsy findings demonstrate that the characteristic histological picture of acute, diffuse glomerulonephritis may sometimes occur with minimal urinary abnormalities and in the absence of symptoms. In tropical Africa, where oedema is such a common symptom, it is even more likely that mild cases of nephritis will be overlooked unless urinalysis becomes established as a routine investigation of sick children. Hendrickse and Gilles (1963) have remarked upon the difficulties which this theoretically simple procedure may entail in an underdeveloped country, and our experience has been similar.

Unfortunately the lack of follow-up, inevitable in a widely scattered rural population who are not yet familiar with the nature of symptomless or latent disease, did not permit an adequate assessment of the prognosis. From our few repeat biopsies it is apparent that the more widespread the initial damage, the longer will the histological abnormalities remain. There is also suggestive but not conclusive evidence that patients with Grades II or IV damage had progressive disease.

Concepts of streptococcal infections and their sequelae, in tropical Africa, are now changing. Several decades ago acute rheumatism was regarded as rare in East Africa (Donnison, 1928; Williams, 1939) but more recently Shaper and Shaper (1958) claimed that chronic rheumatic heart disease formed the largest group of cardiac admissions to Mulago Hospital in 1957. More than a decade ago Jelliffe and Reed (1953) found a β-haemolytic streptococcal carrier rate of only 0.97% among healthy Nigerian children; recently, however, Collard (1961) has reported an incidence of 10% among patients admitted to University College Hospital, Ibadan. Luder (1957), referring to his experience in Uganda during the years 1954–56, states that, 'The haemolytic streptococcus, though present, is relatively avirulent. Tonsilitis and rheumatic fever are rare, and acute nephritis extremely rare'. But a recent community survey conducted in Uganda (G. A. Saxton, 1963, personal communication) has revealed that 20% of rural African schoolchildren are carriers of β-haemolytic streptococci, while our own observations indicate that acute post-streptococcal nephritis is by no means uncommon in Uganda. These findings may have some bearing on the frequency of chronic proliferative glomerulonephritis noted in earlier necropsy reports (Hennessey, 1939; Davies, 1949) and on the more recent observations of Leather (1960) and Hutt and Sood (1963) that the morbidity and mortality from chronic glomerulonephritis is high in patients between 10 and 40 years old.

Summary

The clinical and pathological features of 24 East African children suffering from acute diffuse glomerulonephritis, and studied by means of renal biopsy, are described. The diagnostic pathological criteria were (a) diffuse proliferation and swelling of glomerular endothelial cells, and (b) infiltration by polymorphonuclear leucocytes. Serological evidence of β-haemolytic streptococcal infection was obtained in 75% of cases. The age incidence is lower than that found in temperate climates. A case of post-streptococcal neonatal nephritis, simulating nephrosis, is described.

The clinical pattern was varied; only 14 children had 'haemorrhagic' nephritis; 4 presented as nephrotic syndrome, and 3 with cardiac failure, but malnutrition and hookworm infection were contributory factors in most cases; 3 were detected only on routine urinalysis.

Hypertension, macroscopic haematuria, heavy proteinuria, and raised ASO titres were prevalent where histological changes were more severe. Widespread interstitial and tubular lesions, associated with numerous epithelial crescents and seen within two weeks of onset in two patients, probably denote a progressive lesion.

In contrast to previous reports, it is evident that acute, post-streptococcal nephritis is common in Uganda.

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ACUTE GLOMERULONEPHRITIS IN EAST AFRICAN CHILDREN


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